February 23, 1953

Dr. Lawrence Weed
Bacteriology Dept.
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Washington 12, D.C.

Dear Dr. Weed:

I hasten to answer your letter of the 9th, realizing its urgency to you. However, I have only recently returned from a visit to the Communicable Disease Center at Chamblee, and could not reply sooner. By the way, I ran into Sidbury down there-- in fact, he brought up your work when I (perhaps prematurely) generalized during a lecture there that there was not clearly proven case of drug-induced, heritable resistance in bacteria. He had the mistaken impression that I would be familiar with your work through personal conversation: I wish this were true.

I think the reviewer was rather hard on you, but was justifiably provoked by some of the same perturbations of which I complained in my letter of the 14th. If the paper had stuck to the findings themselves, rather than claimed a new, unexplored territory I think it would have been acceptable even without adequate proof of the origin of the variants. But the paper starts and ends taking this for granted, howbeit there are some qualifications in the middle. But I don't propose to make another critique now. To answer your questions more explicitly:

1) This sounds as if you thought I reviewed your paper. I did not.
2) The notion of using streptomycin-resistance would be to set up artificial mixtures of B/S and B/Cu, using the /S as a marker to distinguish the scv that developed later from those introduced in the beginning. This would permit one to evaluate the selective advantage of B/Cu over B in the presence of Cu. But I would have to know a good deal more detail about the system to suggest whether it would be possible to do a critical experiment.
3) On the whole, I think it would be better to wait until some of the more obvious experiments are done. Your experiment of adding a relatively small number of cells to Cu medium (p. 5) would probably provide the best test. If the inoculum had no scv., and if scv. developed from a small inoculum which never grew appreciably, you would already have a strong case. Beyond this would depend on your own judgment; I would still be circumspect about claiming induction.
4) Still the DNA and RNA per cell is still the most important point. Morse & Carter would be worth looking at. More important, the DNA:RNA ratio has been reported to vary considerably with different growth phases of the same culture.(Boivin; Heden)This kind of work makes anything less than a full cytochemical correlation seem possibly trivial. My trouble with this section was that I couldn't figure out just what kind of trouble you were having.

5) The UV business seems OK to me as a preliminary mention. It doesn't seem to lead anywhere in this paper, however. It might have been better either to cut it to a brief mention, or to do a somewhat more thorough job (following the Reviewer's suggestion of looking at Witkin's paper). But I would not have made such a point of this incidental matter.

6) It does badly need to be referred to a cytochemical basis.

F) Here I disagree with the reviewer. Ephrussi's work is a methodological model for yours. If you could present such convincing proof of induction as he has done, you would be making an outstanding contribution to bacterial genetics.

As to the general picture, may I make two suggestions:

1) do the not very complex experiments suggested above under 3), and see how they shape up as evidence bearing on induction.

2) write the paper over again a little differently, beginning with the observations, and avoiding even such barely connotative terms as transformation. In the discussion (and not the text) discuss the evidence for and implications of induction by Cu.

Is there any chance your E. coli B is something else? Two things make me suspicious of it: 1) Ewing almost fell over when I said someone had done an O and K determination on it: "if this ever was a serologically complete coli, it isn't now"— of a culture straight out of Luria's lab, and 2) in a couple of admittedly casual trials, I did not get any scv using our E. coli B. This brings up another point. Despite your hectic schedule, do you think you still might care to visit this lab for a few days? We could discuss some of your problems considerably better, and you could perhaps get some other ideas and techniques from us in exchange for a demonstration of your result. Nearly any time between now and the middle of May would do on our side, in spite of the remodelling going on.

Yours sincerely,

Joshua Lederberg

P.S. May I keep the ms. a little while? I'll return it immediately on request.